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Ceftolozane-Tazobactam Pharmacokinetics in a Critically Ill Patient on Continuous Venovenous Hemofiltration

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Extended-infusion ceftolozane-tazobactam treatment at 1.5 g every 8 h was used to treat multidrug-resistant *Pseudomonas aeruginosa* in a critically ill patient on continuous venovenous hemofiltration. Serum drug concentrations were measured at 1, 4, 5, 6, and 8 h after the start of infusion. Prefilter levels of ceftolozane produced a maximum concentration of drug (C_{max}) of 38.57 µg/ml, concentration at the end of the dosing interval (C_{min}) of 31.63 µg/ml, time to C_{max} (T_{max}) of 4 h, area under the concentration-time curve from 0 to 8 h (AUC_{0-8}) of 284.38 µg · h/ml, and a half-life ($t_{1/2}$) of 30.7 h. The concentrations were eight times the susceptibility breakpoint for the entire dosing interval.

Ceftolozane-tazobactam is a novel oxyimino-aminothiazolyl cephalosporin and β-lactamase inhibitor used in the treatment of multidrug-resistant Gram-negative organisms, including *Pseudomonas aeruginosa*. The pharmacokinetic and safety profiles of this antibiotic have been established in healthy adults and subjects with various degrees of renal function (1, 2). However, there are currently no data guiding its use when administered as an extended infusion in critically ill patients receiving continuous venovenous hemofiltration (CVVH). The aim of this report was to evaluate the adequacy of extended-infusion ceftolozane-tazobactam to achieve target pharmacokinetic and pharmacodynamic goals in a critically ill patient on CVVH.

We describe here a 61-year-old male (height, 167 cm; weight, 78.8 kg) admitted to the medical intensive care unit (MICU) with moderate acute respiratory distress syndrome, secondary to septic shock. The patient was receiving ceftolozane-tazobactam for a multidrug-resistant *P. aeruginosa* prosthetic hip joint infection, which was diagnosed by intraoperative culture. This strain had an MIC of 1.5 µg/ml to ceftolozane-tazobactam. During the course of treatment, the patient developed acute kidney injury and was started on CVVH, using a Gambro Prismaflex machine with a Prismaflex M150 set AN69HF 1.5-m² hollow-fiber membrane, with a blood flow of 250 ml/min and a dialysate flow of 2 liters/h.

Ceftolozane-tazobactam was administered intravenously at a dose of 1.5 g every 8 h, with an extended-infusion time of 4 h to achieve a pharmacokinetic and pharmacodynamic target of free-drug concentration above the MIC throughout the dosing interval (100% $fT_{>MIC}$). Informed consent was obtained from the patient's family and this was exempted by our institutional review board. After the start of the third CVVH-adjusted infusion, serial prefilter and postfilter blood samples were collected in heparinized tubes at 1, 4, 5, 6, and 8 h after the start of infusion. The samples were centrifuged at 2,500 rpm for 10 min to yield at least 1 ml of plasma. Plasma samples were stored at −80°C until the assay. Ceftolozane and tazobactam concentrations were quantified using previously validated high-performance liquid chromatography (HPLC) methods (C. A. Sutherland and D. P. Nicolau, unpublished data).

Pharmacokinetic parameters for ceftolozane and tazobactam were estimated from the observed plasma concentrations (prefilter) via noncompartmental analysis with the validated WinNonlin software version 6.4 (Pharsight Corporation). The following parameters were reported: maximum concentration of drug (C_{max}), time to C_{max} (T_{max}), concentration at the end of the dosing interval (C_{min}), and area under the concentration-time curve from 0 to 8 h (AUC_{0-8}). The AUC_{0-8} was estimated using linear-up/log-down calculation method. Half-life ($t_{1/2}$) was calculated using the formula 0.693/(−slope). The slope was estimated using the last three time points of the concentration-time profile. Furthermore, the extraction ratios (as a percentage) for both ceftolozane and tazobactam were calculated at each time point using the following formula: extraction ratio = ([concentration$_{prefilter}$ − concentration$_{postfilter}$]/concentration$_{prefilter}$) × 100. The mean and standard deviation extraction ratio was reported.

Lab tests, vital signs, and clinical status of the patient were monitored for adverse events related to ceftolozane-tazobactam.

Using the prefilter levels of ceftolozane after the third dose, a C_{max} of 38.57 µg/ml, C_{min} of 31.63 µg/ml, T_{max} of 4 h, AUC_{0-8} of

TABLE 1 Prefilter ceftolozane-tazobactam drug levels[a]

Time after start of infusion (h)	Ceftolozane concn (µg/ml)	Tazobactam concn (µg/ml)
1	36.67	10.94
4	38.57	9.83
5	33.24	8.39
6	35.57	8.28
8	31.63	7.81

[a] Prefilter levels were drawn from a central venous catheter.

TABLE 2 Postfilter ceftolozane-tazobactam drug levels[a]

Time after start of infusion (h)	Ceftolozane concn (µg/ml)	Tazobactam concn (µg/ml)
1	24.52	6.37
4	34.32	8.78
5	27.61	7.43
6	34.09	7.80
8	30.72	7.30

[a] Postfilter levels were drawn from a port after the filter on the Prismaflex device.

284.38 mcg · h/ml, and $t_{1/2}$ of 30.7 h were estimated. The mean ± standard deviation (SD) extraction ratio for ceftolozane was 13.6% ± 12.3%. Similarly, for tazobactam after the third dose, a C_{max} of 10.94 µg/ml, C_{min} of 7.81 µg/ml, T_{max} of 1 h, AUC_{0-8} of 74.01 µg · h/ml, and $t_{1/2}$ of 28.1 h were estimated. The mean ± SD extraction ratio for tazobactam was 15.2% ± 15.0% (3). The concentration of ceftolozane was eight times the susceptibility breakpoint of 4 µg/ml over the entire dosing interval. The drug levels for ceftolozane-tazobactam are reported in Table 1 and 2 and Fig. 1. The patient did not experience any adverse events related to ceftolozane-tazobactam.

To our knowledge, this report is the first documentation of a patient receiving extended-infusion ceftolozane-tazobactam therapy while on CVVH. Having no guidance for the use of this antibiotic in similar patient populations, we extrapolated data from a current study using ceftolozane-tazobactam at a dose of 3 g every 8 h for ventilated nosocomial pneumonia, which is higher than the currently recommended doses for urinary tract

and intra-abdominal infections, and from piperacillin-tazobactam and cefepime CVVH studies to estimate an appropriate dose for our patient. At the time of antibiotic selection, the patient was experiencing septic shock, and it was known that multidrug-resistant *P. aeruginosa* had been isolated, although MIC data were still being processed. Additionally, it was unknown how well the antibiotic penetrated the site of infection, given the overall limited data for this newer agent. Therefore, using the higher dose of ceftolozane-tazobactam at a dose of 3 g every 8 h from the ongoing pneumonia study in patients with normal renal function, the dose was adjusted to 1.5 g every 8 h to account for renal function since our patient was on CVVH (4–6). We also chose an extended-infusion administration in order to optimize the time that serum free-drug concentrations were above the MIC, given that β-lactam antibiotics exhibit time-dependent antibacterial activity.

In this study, we prospectively measured the systemic pharmacokinetics of ceftolozane and tazobactam in a critically ill patient on CVVH. The patient achieved a lower C_{max} than seen in healthy patients; however, the AUC was greater in our patient than that in healthy patients, potentially due to decreased drug clearance. The lower C_{max} is expected, given the use of a 4-h extended infusion in this patient. The CVVH extraction ratio was low and is similar to the CVVH clearances found with cefepime (7).

Since β-lactam antibiotics have time-dependent antibacterial activity, the primary pharmacokinetic/pharmacodynamic target is the time that serum free-drug concentrations remain above the MIC of the infecting pathogen. The goal $fT_{>MIC}$ for cephalosporins should be at least 40% of the dosing interval,
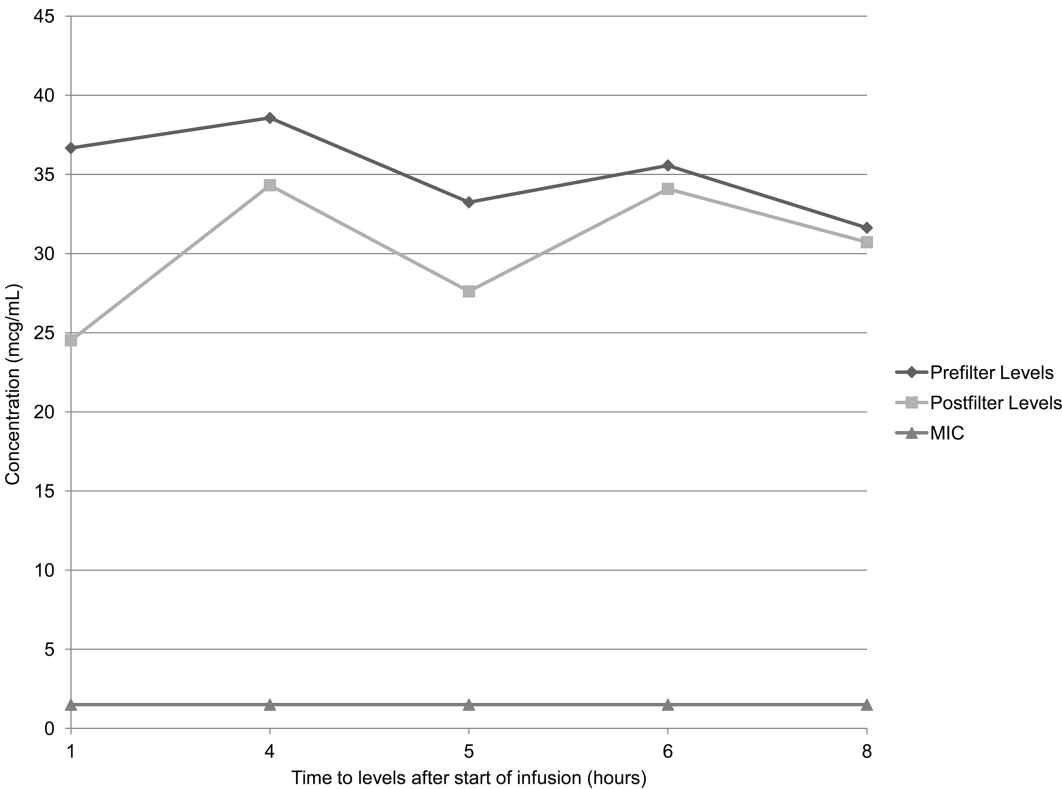

FIG 1 Ceftolozane drug levels in relation to MIC. Prefilter levels were drawn from a central venous catheter. Postfilter levels were drawn from a port in the line after the filter on the Prismaflex device.

although an $fT_{>MIC}$ of 100% may be desirable for optimal outcomes in critically ill patients (8–10). Assuming 20% protein binding for ceftolozane, the lowest free-drug concentration of ceftolozane was the postfilter concentration drawn 1 h into the infusion, at 19.6 μg/ml (3). All estimated plasma free-drug concentrations achieved the pharmacodynamic goals and remained well above the isolated organism's MIC of 1.5 μg/ml and above the susceptibility breakpoint of 4 μg/ml throughout the dosing interval; however, we cannot comment on the concentrations at the site of infection (3). Although relatively high and sustained concentrations of ceftolozane were achieved in this patient, no adverse events related to the drug were observed. Despite adequate treatment of the targeted infection, the patient expired from multiorgan dysfunction.

Our study has a few limitations. First, both pre- and postfilter concentration levels for ceftolozane were higher at 6 h after the start of infusion than they were at 5 h; this is without explanation and might affect our AUC calculations. Second, drug levels were drawn in a patient on CVVH; thus, it is difficult to apply our data to patients on CVVH with different blood and dialysate flow rates or other types of continuous renal replacement therapy (CRRT). Third, the concentrations in the elimination phase were not available; thus, the half-life was calculated utilizing the data from the last three time points (5, 6, and 8 h) for ceftolozane and tazobactam. Complete elimination phase data need to be characterized to confirm the estimate of half-life for ceftolozane and tazobactam during CVVH, which was not clinically feasible in this patient. Given the limitations of the data we obtained, the half-life data should be interpreted with caution.

The data obtained in this investigation provide clinicians with initial guidance for choosing an optimal dosing regimen for ceftolozane-tazobactam in critically ill patients receiving CVVH. Given that the lowest estimated free-drug concentration was 5-fold greater than the susceptibility breakpoint, the estimated half-life was 28 h, and a low extraction ratio was observed in this study, a lower total daily dose might be utilized, and an extended-infusion time may not be necessary for patients on CVVH. As the impact of continuous renal replacement therapy (CRRT) on the clearance of drug can vary markedly, larger studies are needed to verify the optimal dosing strategy for ceftolozane-tazobactam in critically ill patients receiving CVVH and other modalities of CRRT.

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